Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Atrial fibrillation in COVID-19 patients receiving remdesivir, matched case-control analysis

Dear Editor,

We have read with great interest the review article by Chen et al. [1] summarizing concerns regarding atrial fibrillation (AF) in COVID-19 patients. Although no remdesivir related concerns were highlighted by the authors, it should be noted that bradycardia has been consistently associated with remdesivir [2] and patients able to develop bradycardia might have a good prognosis with less respiratory deterioration and lower mortality [3]. Post-infusion electrocardiogram (ECG) changes in QRS axis deviation have also been reported, however the meaning of these changes is uncertain [4]. In abscence of robust data on cardiovascular risks associated with remdesivir, especially related to AF, we aimed to investigate how remdesivir affected survival in patients with AF.

We retrospectively evaluated 5959 consecutively hospitalized COVID-19 patients treated at institution (University Hospital Dubrava, Zagreb, Croatia) from 3/2020 to 6/2021. All patients were Caucasian. Among them, 876 received remdesivir and were compared to a control group of 876 age-, sex-, Charlson-comorbidity-index (CCI)- and COVID-19-severity on-admission- matched patients. Because remdesivir was given to respiratory deteriorating patients, matching was performed step-wise depending on maximal oxygen-requirement (patients receiving remdesivir during mechanical ventilation (MV) were matched with patients who required MV, followed by high-flow oxygen therapy (HFOT) etc). Majority of patients received prophylactic LMWH and corticosteroids. AF was considered if documented prior to or during hospitalization. Mortality was assessed during hospitalization. MedCalc statistical program ver 20.014 (MedCalc Software Ltd., Ostend, Belgium) was used for all statistical procedures. *P* values <0.05 were considered statistically significant.

Among 1752 evaluated patients (876 remdesivir and 876 matched controls), there were 188 (10.7%) patients with AF, similarly distributed between remdesivir and control group (10 vs 11.4%, respectively, $P = 0.354$). Median age was 66 years (65 vs 66 years in remdesivir vs controls; $P = 0.109$), median CCI was 3 points (3 vs 3 points in remdesivir vs controls; $P = 0.115$). A total of 61.8% of patients were male (61.8% vs 61.8% in remdesivir vs controls; $P = 1.000$), 516 (29.5%), received beta blockers (28.2% vs 30.7% in remdesivir vs controls; $P = 0.249$) and 1716 (97.9%) had severe or critical COVID-19 at admission (97.9% vs 97.9% in remdesivir vs controls; $P = 1.000$). During hospitalization 646 (36.9%) patients required HFOT and 493 (28.1%) required MV support. A total of 552 (31.5%) patients died.

Patients with AF experienced significantly worse mortality in comparison to controls (50.5% vs 29.2%; $P < 0.001$) whereas remdesivir use was associated with improved survival in an overall cohort of patients (29.2% vs 33.8%; $P < 0.001$) as shown in Fig. 1. There was a significant interaction between remdesivir use, AF and in-hospital mortality ($P < 0.001$). AF showed less detrimental association with increased mortality in remdesivir (43.2% vs 27.7%; OR 1.98, 95% CI (1.27–3.12), $P < 0.001$) than in control group of patients (57% vs 30.8%; OR 2.97, 95% CI (1.95–4.55), $P < 0.001$). Considering timing of remdesivir application, benefits of remdesivir use in patients with and without AF were evident only in the subgroup of patients receiving remdesivir prior to HFOT or MV ($P < 0.05$ between remdesivir and controls in both patients with and without AF; Fig. 2A), whereas similar mortality rates were present in patients with and without AF when remdesivir was given during HFOT or during MV ($P > 0.05$ between remdesivir and controls in both patients with and without AF; Fig. 2B and C, respectively).

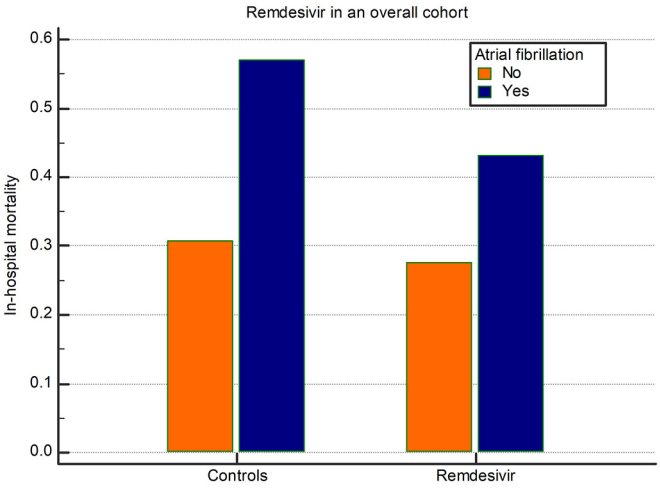

Fig. 1. In-hospital mortality stratified according to remdesivir use and the presence of atrial fibrillation.

There are several important points we would like to emphasize. There is no evidence of improved survival with remdesivir in the randomized controlled setting [5]. Also, there are uncertainties in everyday practice whether remdesivir can safely be given to AF patients due multiple reports of bradycardia and other potentially fatal arrhythmias in COVID-19 patients. However, our matched case-control retrospective study based on a large real-life sample of COVID-19 patients suggests that remdesivir, if given during lower oxygen level requirement, might be associated with improved survival. Despite AF patients experiencing higher mortality rates, remdesivir seems to moderate this association. Mechanisms behind this observation are uncertain, but could be attributable to both antiviral effects of the drug and improved heart rate control in patients with AF. Bradycardia during remdesivir treatment was reported to occur similarly in patients with and without AF, and to be associated with less respiratory deterioration and improved survival [3]. Benefits of remdesivir use in both AF and

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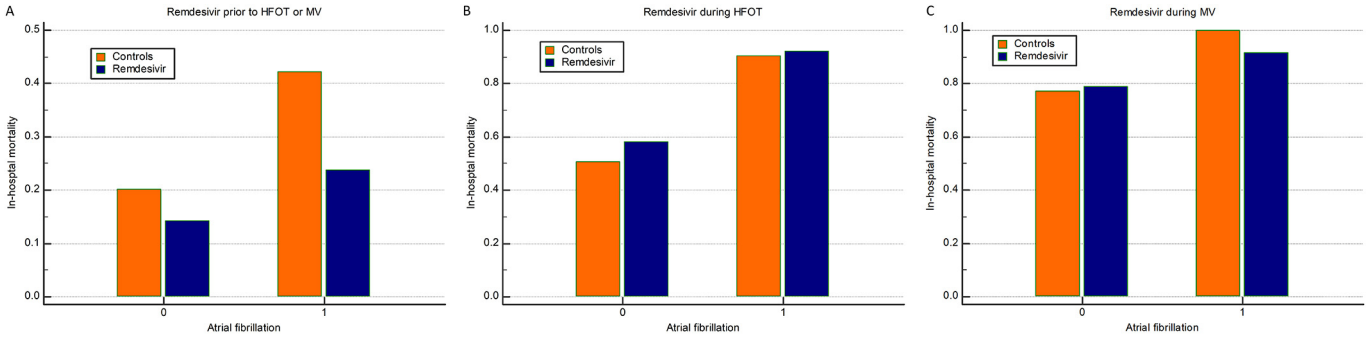

Fig. 2. In-hospital mortality stratified according to the presence of atrial fibrillation and remdesivir use considering the level of oxygen demand at the time of remdesivir application: A) before high flow oxygen therapy (HFOT) or mechanical ventilation (MV) requirement, B) during HFOT and C) during MV.

non-AF patients are evident only if drug is given prior to HFOT or MV respiratory support.

Limitations of our work are single center experience and retrospective study design. Our results are representative for treatment of severe or critical COVID-19 patients in a high output tertiary level institution and might not be generalized to other clinical contexts. Nevertheless, this is the first report on the favorable role of remdesivir in patients with AF. Our results encourage remdesivir use in this subgroup of patients who seem to especially benefit if the drug is used before HFOT or MV support is required.

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Authorship contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Petra Bistrovic, Sime Manola, Ana Jordan, Ivan Papic, Maja Ortner Hadziabdic and Marko Lucijanic. The first draft of the manuscript was written by Petra Bistrovic and Marko Lucijanic and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval

The study was approved by the University Hospital Dubrava Review Board (nm. 2021/2503-04).

Credit authorship contribution statement

Petra Bistrovic: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Sime Manola:** Data curation, Supervision, Validation, Writing – review & editing. **Ivan Papic:** Data curation, Supervision, Validation, Writing – review & editing. **Ana Jordan:** Data curation, Supervision, Validation, Writing – review & editing. **Maja Ortner Hadziabdic:** Data curation, Supervision, Validation, Writing – review & editing. **Marko Lucijanic:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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